Journal of Forensic and Legal Medicine 19 (2012) 245–249

Contents lists available at SciVerse ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Review

Postmortem drug concentration intervals for the non-intoxicated state – A review

Kristian Linnet MD, DMSci, Head, Professor *

Section of Forensic Chemistry, Department of Forensic Medicine, Faculty of Health Sciences, University of Copenhagen, Frederik Femte Vej 11, DK-2100 Copenhagen Ø, Denmark

ARTICLE INFO

Article history:
Received 23 November 2011
Received in revised form
16 January 2012
Accepted 13 February 2012
Available online 7 March 2012

Keywords:
Postmortem
Forensic
Toxicology
Reference intervals

ABSTRACT

In postmortem toxicology, it is important to know what the usual drug level is in blood under ordinary therapy to make correct interpretations with regard to the possible occurrence of poisoning. A commonly used source is The International Association of Forensic Toxicologists (TIAFT) list of drug concentrations providing therapeutic drug levels, usually measured in serum. In this article, published postmortem-derived blood drug reference concentration intervals were related to therapeutic serum levels of drugs from the TIAFT list to assess agreement or discrepancies with focus on the importance of postmortem redistribution. The ratio between the upper limits was evaluated. This ratio ranged from 0.13 to 11.3 for 57 compounds with a median value of 1.5. For about a third of the compounds the ratio exceeded three. There was a tendency that for highly water-soluble drugs with a low propensity for redistribution, the ratio was generally low. For example, for pentobarbital, carisoprodol, meprobamate, carbamazepine, phenazone and theophylline, the ratio ranged from 0.14 to 1.1 with a median of 0.4. For the 15 antidepressants considered, on the other hand, the ratio was relatively high, ranging from 0.6 to 4.7 (median 2.4). For antipsychotics, the ratio ranged from 0.2 to 11.3 with a median of 1.4. In conclusion, there were generally wide discrepancies between serum-based intervals as presented in the TIAFT list and published postmortem blood-based drug reference intervals. More focus on postmortem-derived intervals is encouraged, so that those that have been estimated are cited in reference publications and so that further intervals are estimated. Ultimately, a reliable database of postmortem blood-based drug reference intervals for use by the forensic community is desirable.

1. Introduction

To interpret postmortem drug concentrations in blood or tissues it is important to have knowledge of the concentrations usually observed under therapeutic conditions. Commonly, plasma or serum concentrations observed *in vivo* under therapeutic circumstances or in pharmacokinetic studies are used as reference concentrations. For example, the concentrations referring to the therapeutic situation displayed in The International Association of Forensic Toxicologists (TIAFT) listing of reference blood levels[1] are serum concentrations, and in compilations of drug concentrations for forensic use, the references to the therapeutic situation usually are based on *in vivo* studies, see, for example, the handbook by Baselt and the compilation by Schulz and Schmoldt.[2,3] By referring to *in vivo* conditions, the phenomenon of postmortem redistribution is not taken into account.[4,5] In addition, a possible discrepancy between plasma/serum and full blood concentrations is not considered.[6] In a few compilations and some studies on specific drugs, reference is provided to postmortem drug concentrations for the therapeutic situation, or more precisely, the presumed non-intoxicated state.[7–17] Druid and Holmgren present the most comprehensive compilation with 83 drugs and/or metabolites from various drug classes. Reis et al. present a compilation of 15 antidepressants with metabolites. The other studies concern single compounds mostly of the psychoactive type. Thus, postmortem-derived reference intervals are available only for a limited number of compounds. This may appear somewhat surprising, since there has been so much focus on the phenomenon of postmortem redistribution over the years.[4,5,18] Much attention has been given to the group of antidepressants, where measurements before and after death, supplemented by experimental studies, have pointed in the direction that postmortem levels exceed antemortem levels by several folds.[5,18,19] The differences are most pronounced in the central vessels and heart, and much focus has been directed on the heart/femoral vein concentration ratio.[20] Although this ratio is of interest as an indicator of the degree of postmortem redistribution, in the postmortem situation it is the actual intervals observed in a peripheral vein corresponding to the intoxicated and non-intoxicated situations that are of primary relevance when considering cases. In this overview, focus is on the

* Tel.: +45 35326100; fax: +45 35326085.
E-mail address: kristian.linnet@forensic.ku.dk.

1752-928X/$ – see front matter © 2012 Elsevier Ltd and Faculty of Forensic and Legal Medicine. All rights reserved.
doi:10.1016/j.jflm.2012.02.010

relations between postmortem and *in vivo* concentrations for the presumed non-intoxicated situation.

2. Factors of importance for interpreting postmortem measurements in relation to published *in vivo* serum levels for the presumed non-intoxicated situation

2.1. Analytical methodology

Variation in analytical technology may result in differences between actual measurements and reports in the literature. Differences are expected over time related to the development of more sensitive and specific measurement methods. In addition, different measurement principles are likely to cause differences, for example, chromatographic versus immunological techniques. However, most drug assays are based on chromatographic principles and so methodological differences may not be a major confounder when comparing *in vivo* with postmortem measurements. Nevertheless, when comparing older measurements in the literature with actual measurements, improvement in analytical methodology may be a confounding factor.

2.2. Drug stability and in vitro conversions

Some compounds are likely to be degraded in the postmortem state. Nitrobenzodiazepines are converted by bacteria to amino-compounds.[21] Some compounds such as cocaine and zopiclone are generally unstable, and the postmortem situation will then be likely to exert a greater impact, because of the less-controlled conditions for blood during a variable time period between death and blood sampling.[6,7,22] Also, in case of extensive putrefaction and body decomposition, blood may not be available or may be of a poor quality, so that drug measurements generally become unreliable. However, generally, most compounds are fairly stable when the postmortem samples have been taken with added fluoride and are stored in the frozen state.

2.3. Single dose versus steady state

For new drugs, reference may be taken to serum concentrations observed in initial pharmacokinetic studies based on only single doses. These levels will generally tend to be low compared to the situation with repeated dosing, that is, the steady-state situation with some drug accumulation.[23]

2.4. Time of sampling in relation to intake of dose

In postmortem cases, trough values are generally not obtained as under the *in vivo* therapeutic drug-monitoring situation. This factor should also be taken into account. When dosing twice during one half-life interval, for example, every 12 h for a drug with a half-life of 24 h, the difference between minimum and maximum concentrations amounts to about 40% under first-order kinetics.[23] When the dosing interval equals the half-life, the factor is about 2, that is, peak values exceed trough values by 100%. Thus, published trough values should then be doubled to take this fact into account, when dealing with the postmortem situation, where no controlled timing is present.

2.5. Inter-individual variation/presentation of published data

Generally, there is a wide variation in drug turnover rate from subject to subject. Thus, for standard doses, the range of serum concentrations observed is considerable. In some reference tables or books, only mean values are provided, not the total range, which is a factor tending to underestimate the total reference range under therapeutic conditions. In addition, for new drugs the number of subjects having been studied may be limited, so that the total range of concentrations observed under therapeutic conditions is likely to be underestimated.

2.6. Blood/serum concentration ratio

For most drugs, the distribution between the water phase and the erythrocytes is fairly even, so that the difference between serum and full blood measurements in itself is of minor importance.[6] However, for some compounds there may be a considerable difference. If a compound only penetrates into the erythrocytes to a limited degree, the serum measurements exceed the full blood measurements. This is the case, for example, THC and carbamazepine, resulting in serum concentrations equal to up to two times full blood concentrations.[6,7] Few compounds, on the other hand, are accumulated in the erythrocytes resulting in a reversed picture, for example, acetazolamide and chloroquine.[6]

2.7. Usual dose range

Initial pharmacokinetic studies may be based on smaller doses than those being gradually adopted in clinical practice. Also, dose ranges may depend on the diagnosis, for example, higher doses (e.g., fourfold) of serotonergic drugs are used for treatment of obsessive–compulsive conditions than for depression.[23] The latter diagnosis will often form the basis for establishment of therapeutic intervals, which then are misleading in relation to cases involving obsessive–compulsive disorders. For anaesthetic drugs, it should be clarified whether a stated interval refers to full anaesthesia with presumed assisted ventilation, or whether the reference interval refers to drug abuse. This is of relevance for ketamine and some other drugs.

2.8. Tolerance development

Illegal substances and medical drugs subject to abuse such as opioids are subject to the development of tolerance, which results in the use of higher doses. Supposing linear kinetics, the measured drug concentrations increase proportionally with the dose. In the case of opioids, regular pain treatment may involve increases in daily dose of perhaps up to factors 10–25, and accordingly similar increases in the serum concentrations/postmortem blood concentrations occur.[24] Thus, both in the *in vivo* and postmortem situations, reference intervals are influenced by tolerance development, making the intervals very wide. Tolerance may also play a role for other drugs, for example, antipsychotics. Due to counter-regulation of receptors, patients in chronic therapy adapt to high drug levels that are toxic to drug-naïve subjects. This has been observed for the drug clozapine, where an ordinary dose aimed for a chronic patient induced a fatal intoxication in a drug-naïve patient.[25]

2.9. Atypical response

Atypical or paradox reactions to drugs may lead to 'intoxicated'-like states despite the presence of a usual drug level, for example, benzodiazepines and alcohol.[26] Accidents leading to death may then occur because of bizarre behaviour. Thus, even though a drug concentration is in the usual level, the drug may have been indirectly contributing to death.

2.10. Postmortem sampling conditions

It is generally recommended to use femoral blood. It is important to avoid contamination with central blood. Evaluation of

different sampling techniques has yielded similar results.[27] A systematic study involving duplicate sampling from the femoral veins showed a considerable random sampling variation yielding a preanalytical uncertainty component superseding the analytical variation considerably.[28]

2.11. Postmortem redistribution/diffusion

As mentioned in the introduction, postmortem redistribution and diffusion have been subject to much interest, and it has been well documented that the concentration of many drugs, for example, antidepressants, is likely to be several fold higher in the central vessels and heart than in peripheral veins such as the femoral or subclavian veins.[4,5,20] Further, perimortem measurements have shown that postmortem peripheral vein concentrations are more close to *in vivo* concentrations measured shortly before death.[18,19,29–32] However, the postmortem levels, for example, tricyclic antidepressants in femoral blood may exceed ante-mortem levels in serum by several fold. For example, Hilberg et al.[18] reported a mean ratio of 3.3 between postmortem femoral blood and ante-mortem serum drug concentrations with a 95%-reference range from 1.1 to 6.0. Several experimental studies also show that the concentrations are likely to increase in the postmortem period. The relations for some antipsychotic drugs may be the same as for antidepressants. Flanagan et al. showed that for the pig, there was a mean increase in central vessels for clozapine corresponding to a factor 4.5 and in the femoral vein corresponding to 1.5 times.[33] In a recent case, Flanagan and Ball found clozapine and norclozapine serum concentrations of 0.56 and 0.43 mg l^{-1}, respectively, 1 h before death, whereas postmortem femoral whole blood taken less than 34 h later had concentrations of 3.73 and 1.75 mg l^{-1}, respectively.[34] In a comparison between clozapine postmortem measured blood levels and *in vivo* serum levels for a series of cases, where clozapine was not presumed to be related to the cause of death, an average factor of about 4 was observed.[35] To distinguish between high levels related to an acute overdose as opposed to a high concentration resulting from chronic therapy or a postmortem redistribution artefact, consideration of the drug/metabolite ratio can be valuable.[22,36] In case of tricyclic antidepressants, clozapine or other antipsychotics, a prominent metabolite (often the demethylated drug) will be present, which will be helpful for interpretation. A high ratio points towards acute ingestion, whereas a lower ratio contradicts this event. The usual range of the ratio during chronic therapy should be used as a reference.

The degree of postmortem redistribution is to some extent related to the volume of distribution for a drug, so that lipophilic drugs have a higher tendency to be redistributed than hydrophilic drugs, because the former have higher tissue concentrations.[22,37] The tricyclic antidepressants and many antipsychotic drugs have high volumes of distribution and are generally subject to a considerable degree of redistribution. On the other hand, drugs that are more water soluble with small volumes of distribution, for example, many antiepileptics, morphine, paracetamol, salicylate and others, are not likely to have increased postmortem blood levels. Actually, some drugs may have decreased levels in postmortem femoral blood compared to *in vivo* serum levels because of a blood/serum distribution ratio below unity, for example, carbamazepine.[32]

2.12. Random statistical variation

Many intervals are based on measurements from relatively few subjects, which results in a considerable statistical uncertainty with regard to estimated interval limits. This pertains to both *in vivo* and postmortem estimated reference concentrations.[38]

3. Limitations of postmortem-derived drug reference intervals

Postmortem-derived reference intervals are based on cases, where the case story points towards other causes of death than intoxication by the given drug in question. The criteria can be more or less stringent. In the cited Swedish studies, it has been required that the deceased demonstrated the ability to perform a complex task just before death, that is, was able to hang himself. If the cause of death is a traffic accident, it may be unclear whether the deceased was under influence of the drug or not. Thus, in the postmortem situation, there may be uncertainties with regard to interpretation of the situation. Thus, even though only 'clear-cut' cases are selected from a large material for establishment of postmortem reference intervals, some cases may represent false classifications. A further complication is that in many cases several drugs are present and/or alcohol. Whether a given drug then is involved as a contributing factor may be unclear.

4. Postmortem reference intervals for the non-intoxicated state in relation to serum concentrations under presumed therapeutic conditions

Among publications dealing with postmortem-derived reference intervals for the non-intoxicated state, Druid and Holmgren[7] provided the most comprehensive source with a listing of 83 compounds, inclusive of metabolites. In a later Swedish study, postmortem-derived intervals for 15 antidepressants with metabolites were presented.[8] In addition to these studies, nine other studies dealing with single compounds were found.[9–17] In some of the publications, the number of reference cases was very low, for example, 3, and these are not included in the comparison. If the same compounds were covered by several publications, the one based on the highest sample size was included. Some obsolete compounds in the listing of Druid and Holmgren were omitted, and there were some overlaps between the compounds listed in the publications. Thirty-five of the compounds studied by Druid and Holmgren were included. Concerning serum concentrations, one may find several, sometimes many studies related to *in vivo* therapeutic/pharmacokinetic conditions. To get an impression of what

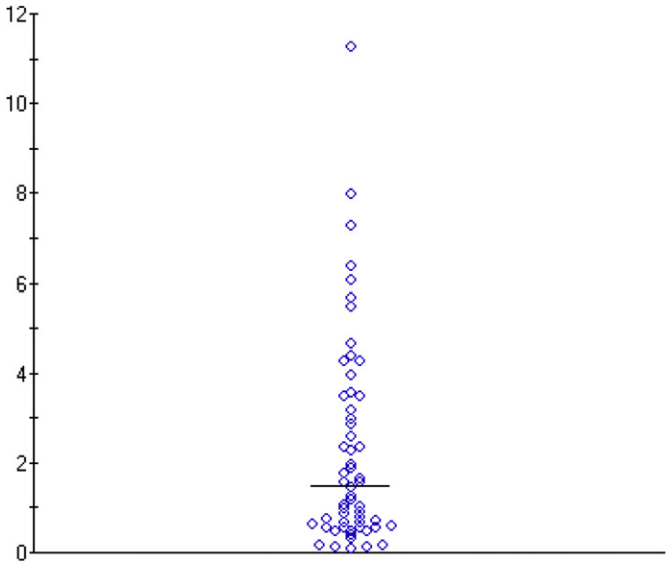

Fig. 1. Distribution of ratio between upper postmortem reference limit and upper TIAFT reference interval limit for 57 drugs.

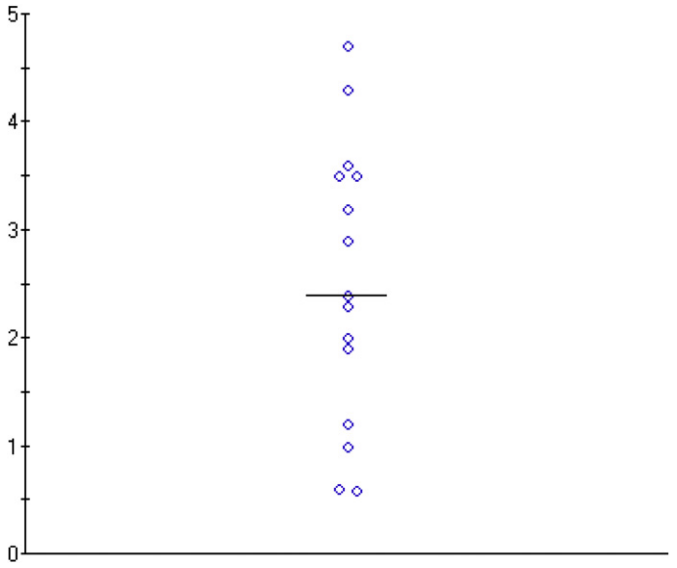

Fig. 2. Distribution of ratio between upper postmortem reference limit and upper TIAFT reference interval limit for 15 antidepressants.

values may often form the basis for reference in forensic laboratories, serum concentrations displayed in the TIAFT list were taken as a basis.[1] The values from the *in vivo* serum concentration-based intervals and the postmortem-based intervals were then compared. The ratios between the upper limits of the postmortem-derived intervals and the serum concentration-based intervals from the TIAFT list were primarily assessed. The upper limits may have been computed slightly different in the various publications. Druid and Holmgren give the 90-percentile, unless the sample size is small. Reis et al. and Druid et al. also provide the 90-percentile, and in the other publications it may be the maximum values. In the TIAFT list there is no specification. The ratio ranges from 0.13 to 11.3 for 57 compounds with a median value of 1.5 (Fig. 1). About a third of the ratios exceed three. Thus, there is a considerable variation with a tailing of high ratio values. Although these ratios should not be over-interpreted, there seems to be a tendency that for highly

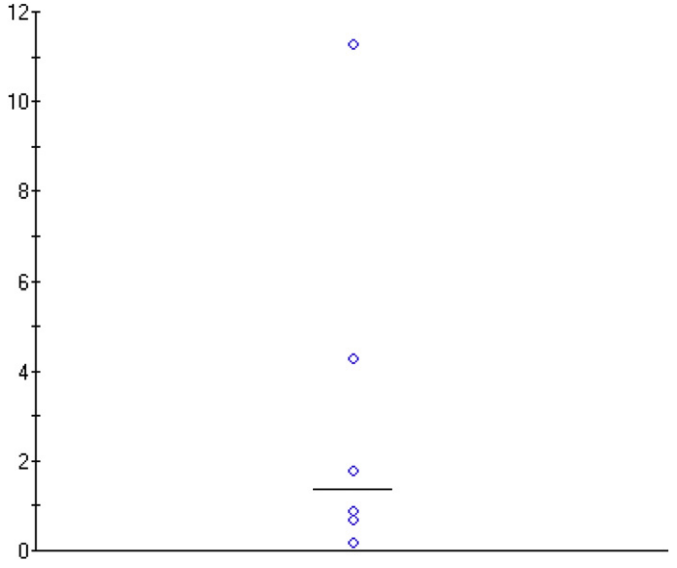

Fig. 3. Distribution of ratio between upper postmortem reference limit and upper TIAFT reference interval limit for 6 antipsychotics.

Table 1
Examples of measured paired postmortem/ante-mortem concentration ratios for various drugs.

Compounds	Ratio (no. of cases)	Reference
Tricyclic antidepressants	1.1–6 ($N = 8$)	18
MDMA	1.1–6.6 ($N = 5$)	31
MDA	1.5–13.3 ($N = 5$)	31
Amiodarone, desethylamiodarone, digoxin, flecainide, sotalol	0.9–3.6 ($N = 1$)	30
Various drugs	1.1–11.7 ($N = 7$)	29
Clozapine	6.7 ($N = 1$)	34
Carbamazepine, phenytoin, phenobarbital	0.16–0.65 ($N = 16$)	32

water-soluble drugs with a low propensity for redistribution, the ratio is generally low. For example, for pentobarbital, carisoprodol, meprobamate, carbamazepine, phenazone and theophylline, the ratio ranged from 0.14 to 1.1 with a median of 0.4. Thus, for these compounds the serum concentration-based intervals on average actually overestimate the limits compared to the postmortem situation. For the 15 antidepressants included in the comparison, on the other hand, the ratio was relatively high, ranging from 0.6 to 4.7 (median 2.4) (Fig. 2). For antipsychotics, the ratio ranged from 0.2 to 11.3 with a median of 1.4 (Fig. 3).

5. Comparisons of ante- and postmortem measurements

Several studies have been undertaken to compare ante- and postmortem measurements in the same subjects (Table 1). With regard to antidepressants, on average three- to fourfold increase in femoral vein concentrations are observed.[5,18] Cook et al. investigated several drug classes and found ratios from 1.1 to 11.7.[29] Elliott considered MDMA and MDA and found ratios between 1.1 and 13.3.[31] O'Sullivan et al. considered cardio-vascular drugs and found ratios 0.9–3.6.[30] The mentioned case regarding clozapine had a ratio of 6.7.[34] For the older group of antiepileptics, the ratio is generally below unity.[32] These drugs have a blood/plasma distribution ratio below 1 and are not subject to postmortem redistribution.

6. Discussion and conclusion

The phenomenon of postmortem redistribution and several of the other mentioned factors of importance for interpretation of postmortem drug reference concentrations tend to result in higher postmortem femoral blood concentrations compared to published *in vivo* serum levels for many drugs. Especially with regard to antidepressants, there has been focus on this aspect. In the publication by Reis et al., one can for the 15 antidepressants investigated look at the ratio between 90-percentiles for postmortem-derived intervals and therapeutic drug-monitoring serum values given in the publication. The median ratio is 3.1 with a range from 1.3 to 7, that is, not so different from the ratios related to the TIAFT concentration upper limits (Fig. 2). With regard to antipsychotics, the ratios shown in Fig. 3 range from 0.2 to 11.3 (median 1.4). Flanagan et al. noticed a ratio of about 4 for clozapine.[35] In this article, though, it was not clarified whether femoral blood samples were taken, and thus the publication is not included as background for Fig. 1, where only the value by Druid and Holmgren are given (ratio for clozapine 1.8). Thus, with regard to antidepressants and some antipsychotics, postmortem drug interpretations are likely to be biased towards the conclusion that some degree of intoxication was present, even though this might not be the case, when using the serum concentration-based intervals. This may contribute to erroneous conclusions with regard to cause and manner of death. Thus,

uncritical use of drug tables based to a large extent on *in vivo* drug reference intervals such as the TIAFT list, the compilation by Schulz and Schmoldt, the handbook by Baselt or others should be discouraged. It will often be appropriate to use upper reference limits several fold higher than those observed *in vivo*.

Regarding drugs of abuse, the development of tolerance makes it difficult to interpret measurements both in the *vivo* and postmortem context. For example, morphine is not subject to postmortem redistribution to any significant extent.[39,40] However, as reviewed by Jung and Reidenberg, very high serum concentrations of opioids may occur in cancer patients during chronic therapy.[24] This phenomenon has been neglected in several legal cases, which has resulted in erroneous accusations of overdosing directed against medical doctors having been responsible for the pain treatment. In the area of drug abuse, it is also well known that there are wide, overlapping intervals of *in vivo* serum concentrations and postmortem levels.[41,42] In the published studies, however, the postmortem levels are generally not separated into intervals, where the drug level is not regarded as contributing or not contributing, and so not included in the listing here. Thus, both with regard to *in vivo* and postmortem concentrations, very high levels of opioids may be within the 'therapeutic' intervals being typical for chronically treated patients or abusers.

For illicit drugs without therapeutic applications, it is not meaningful to operate with a reference interval. However, one may refer to intervals linked to moderate abuse and more severe intoxication, possibly levels often associated with lethal poisonings, respectively. Here the phenomenon of tolerance development leads to wide, overlapping intervals.

In conclusion, when possible, it is recommended to apply properly derived postmortem drug reference intervals, and it is encouraged to establish these intervals for more drugs than currently are available. Although postmortem-derived reference intervals also are subject to some uncertainties and limitations, they generally seem preferable to the use of *in vivo* serum-based intervals that often will tend to be too low. As a starting point, already established intervals could be referenced to a better extent in tables or reference books, and then on the long sight, more drugs could have postmortem reference intervals estimated.

Conflict of interest

None declared.

References

1. Reference blood level of therapeutic and toxic substances. http://www.tiaft.org/toxic_values [accessed 19.09.11].
2. Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. *Pharmazie* 2003;**58**:447–74.
3. Baselt RC. *Disposition of toxic drugs and chemicals in man*. 8th ed. Foster City, California, USA: Biomedical Publications; 2008.
4. Prouty RW, Anderson WH. The forensic science implications of site and temporal influences on postmortem blood-drug concentrations. *J Forensic Sci* 1990;**35**:243–70.
5. Pounder DJ, Jones GR. Post-mortem drug redistribution – a toxicological nightmare. *Forensic Sci Int* 1990;**45**:253–63.
6. Skopp G. Preanalytical aspects in postmortem toxicology. *Forensic Sci Int* 2004;**142**:75–100.
7. Druid H, Holmgren P. A compilation of fatal and control concentrations of drugs in postmortem femoral blood. *J Forensic Sci* 1997;**42**:79–87.
8. Reis M, Aamo T, Ahlner J, Druid H. Reference concentrations of antidepressants. A compilation of postmortem and therapeutic levels. *J Analyt Toxicol* 2007;**31**:254–64.
9. Druid H, Holmgren P, Ahlner J. Flunitrazepam: an evaluation of use, abuse and toxicity. *Forensic Sci Int* 2001;**122**:136–41.
10. Jaffe PD, Batziris HP, Van der Hoeven P, DeSilva D, Path D, McIntyre IM. A study involving venlafaxine overdoses: comparison of fatal and therapeutic concentrations in postmortem specimens. *J Forensic Sci* 1999;**44**:193–6.
11. Kirkton C, McIntyre IM. Therapeutic and toxic concentrations of mirtazapine. *J Anal Toxicol* 2006;**30**:687–91.
12. Parker DR, McIntyre IM. Case studies of postmortem quetiapine: therapeutic or toxic concentrations? *J Analyt Toxicol* 2005;**29**:407–12.
13. Vance C, McIntyre IM. Postmortem tissue concentrations of olanzapine. *J Analyt Toxicol* 2009;**33**:15–26.
14. Molina DK, Hargrove VM. What is the lethal concentration of hydrocodone? A comparison of postmortem hydrocodone concentrations in lethal and incidental intoxications. *Am J Forensic Med Pathol* 2011;**32**:108–11.
15. Linnet K, Steentoft A, Simonsen KW, Sabers A, Hansen SH. An oxcarbazepine-related fatality with an overview of 26 oxcarbazepine postmortem cases. *Forensic Sci Int* 2008;**177**:248–51.
16. Linnet K, Lang LM, Johansen SS. Postmortem femoral blood concentrations of amlodipine. *J Analyt Toxicol* 2011;**35**:227–31.
17. Pricone MG, King CV, Drummer OH, Opeskin K, McIntyre IM. Postmortem investigation of lamotrigine concentrations. *J Forensic Sci* 2000;**45**:11–5.
18. Hilberg T, Rogde S, Mørland J. Postmortem drug redistribution – human cases related to results in experimental animals. *J Forensic Sci* 1999;**44**:3–9.
19. Hilberg T, Bugge A, Beylich K-M, Ingum J, Bjørneboe A, Mørland J. An animal model of postmortem amitriptyline redistribution. *J Forensic Sci* 1993;**38**:81–90.
20. Dalpe-Scott M, Degouffe M, Garbutt D, Drost M. A comparison of drug concentrations in postmortem cardiac and peripheral blood in 320 cases. *Can Soc Forensic Sci J* 1995;**28**:113–21.
21. Drummer OH. Post-mortem toxicology. *Forensic Sci Int* 2007;**165**:199–203.
22. Dinis-Oliveira RJ, Carvalho F, Duarte JA, Remiao F, Marques A, Santos A, et al. Collection of biological samples in forensic toxicology. *Toxicol Mech Meth* 2010;**20**:363–414.
23. Brunton LL, Lazo JS, Parker KL. *Goodman & Gilman's the pharmacological basis of therapeutics*. 11 ed. New York: McGraw-Hill; 2006.
24. Jung BF, Reidenberg MM. Interpretation of opioid levels: comparison of levels during chronic pain therapy to levels from forensic autopsies. *Clin Pharmacol Ther* 2005;**77**:324–34.
25. Stanworth D, Hunt NCA, Flanagan RJ. Clozapine – a dangerous drug in a clozapine-naïve subject. *Forensic Sci Int* 2012;**214**:e23–5.
26. Drummer OH. *The forensic pharmacology of drugs of abuse*. London: Arnold; 2001.
27. Hargrove VM, McCutcheon JR. Comparison of drug concentrations taken from clamped and unclamped femoral vessels. *J Anal Toxicol* 2008;**32**:621–5.
28. Linnet K, Johansen SS, Buchard A, Munkholm J, Morling N. Dominance of preanalytical over analytical variation for measurement of methadone and its main metabolite in postmortem femoral blood. *Forensic Sci Int* 2008;**179**:78–82.
29. Cook DS, Braithwaite RA, Hale KA. Estimating antemortem drug concentrations from postmortem blood samples: the influence of postmortem redistribution. *J Clin Pathol* 2000;**53**:282–5.
30. O'Sullivan JJ, McCarthy PT, Wren C. Differences in amiodarone, digoxin, flecainide and sotalol concentrations between antemortem serum and femoral postmortem blood. *Hum Exp Toxicol* 1995;**14**:605–8.
31. Elliott SP. MDMA and MDA concentrations in antemortem and postmortem specimens in fatalities following hospital admission. *J Analyt Toxicol* 2005;**29**:296–300.
32. May T, Jürgens U, Rambeck B, Schnabel R. Comparison between premortem and postmortem serum concentrations of phenobarbital, phenytoin, carbamazepine and its 10, 11-epoxide metabolite in institutionalized patients with epilepsy. *Epilepsy Res* 1999;**33**:57–65.
33. Flanagan RJ, Amin A, Seinen W. Effect of post-mortem changes on peripheral and central whole blood and tissue clozapine and norclozapine concentrations in the domestic pig (Sus scrofa). *Forensic Sci Int* 2003;**132**:9–17.
34. Flanagan RJ, Ball RY. Gastrointestinal hypomotility: an under-recognized life-threatening adverse effect of clozapine. *Forensic Sci Int* 2011;**206**:e31–6.
35. Flanagan RJ, Spencer EP, Morgan PE, Barnes TRE, Dunk L. Suspected clozapine poisoning in UK/Eire 1992–2003. *Forensic Sci Int* 2005;**155**:91–9.
36. Couchman L, Morgan PE, Spencer EP, Flanagan RJ. Plasma clozapine, norclozapine, and the clozapine: norclozapine ratio in relation to prescribed dose and other factors: data from a therapeutic drug monitoring service, 1993–2007. *Ther Drug Monit* 2010;**32**:438–47.
37. Ferner RE. Post-mortem clinical pharmacology. *Br J Clin Pharmacol* 2008;**66**:430–43.
38. Linnet K. Nonparametric estimation of reference intervals by simple and bootstrap-based procedures. *Clin Chem* 2000;**46**:867–9.
39. Gerostamoulos J, Drummer OH. Postmortem redistribution of morphine and its metabolites. *J Forensic Sci* 2000;**45**:843–5.
40. Logan BK, Smirnov D. Postmortem distribution and redistribution of morphine in man. *J Forensic Sci* 1996;**41**:221–9.
41. Darke S, Sunjic S, Zador D, Prolov T. A comparison of blood toxicology of heroin-related deaths and current heroin users in Sydney Australia. *Drug Alcohol Depend* 1997;**47**:45–53.
42. Milroy CM, Forrest RW. Methadone deaths: a toxicological analysis. *J Clin Pathol* 2000;**53**:277–81.